REMARKS

Claims 1-3, 7, 8 and 11-107 were pending in the present application. Claims 11-42, 43-49, 52-59, 62, 64-70, 73, 76-82, 85 and 87-89 were withdrawn from further consideration as being drawn to non-elected subject matter. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86 and 90-107 were variously rejected under 35 U.S.C. § 112, first paragraph, and § 102(b). Claims 50, 51, 60, 61, 71, 72, 83 and 84 were rejected under 35 U.S.C. § 112, second paragraph.

By this amendment, claims 1, 2, 60, 63 and 75 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification and, for example, at page 36, line 21, and page 43, lines 1-3.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86 and 90-107 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this ground for rejection.

The amended claims are directed to populations of conjugate molecules which are defined by both structural and functional characteristics. The conjugate molecules comprise an antigen and a polynucleotide where the polynucleotide comprises an immunostimulatory sequence (ISS) and is greater than 6 and less than about 200 nucleotides in length. For the population of claim 1, the extent of antigen and polynucleotide conjugation is such that the ratio of conjugate to antigen required for 50% inhibition of antibody to antigen binding is about 3.5 to about 6.0. For the population of claim 2, the extent of antigen and polynucleotide conjugation provides a 40% histamine release ratio of greater than about 500. For the population of claim 63, the extent of antigen and polynucleotide conjugation provides an average of at least 5.5 of the polynucleotides per antigen molecule. For the population of claim 75, the extent of antigen and polynucleotide conjugation provides an average ratio of average polynucleotide mass to average antigen mass of at least 1.1.

The Examiner states that "it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention." Office Action, page 7. Applicants respectfully disagree with this conclusion.

As described on pages 23-24, the claimed conjugate populations fall into the "H" class of conjugate molecules and each of the claimed populations are specifically defined by particular structural and functional features. Applicants respectfully submit that the specification provides sufficient guidance to teach one skilled in the art how to make and use the claimed conjugate populations.

The working examples in the specification (pages 71-86) exemplify populations of the conjugate molecules with functional features as claimed. In addition, examples of ISS-containing polynucleotides and methods for their synthesis are provided, for example, on pages 36-43. Examples of antigens of use in the claimed compositions are provided, for example, on pages 43-50. Examples of ways to couple the ISS-containing polynucleotide and antigen to

generate the claimed conjugate populations are provided, for example, on page 30-32 and 50-53. Means of assessing the structural and functional characteristics of a population of conjugate molecules as claimed are provided, for example, on pages 28-36. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

The Examiner states that the "specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins ..." and that the "term "antigen", "polypeptide" and "allergen" without SEQ ID NO has no structure much less function." Office Action, pages 5-6. Applicants respectfully point out that the specification describes that the "term "antigen" means any substance that is recognized and bound specifically by an antibody or by a T cell antigen receptor." Specification, page 16, lines 19-20. As such, an antigen is a substance which can be identified and understood by one skilled in the art.

Applicants respectfully submit that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is "undue." As the court held in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), the test for enablement does not rest merely on the quantity of experimentation that would be required to practice an invention, "since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Applicants have provided data in the form of working examples that shows how to make and assess the claimed functional characteristics of the conjugate populations.

The court in *In re Wands* found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. With respect to the present invention, polynucleotides containing immunostimulatory sequences were known in the art as

demonstrated, for example, by the many references cited on pages 4-6. In addition, antigens and ways to conjugate an antigen and a polynucleotide were also known. As outlined above, the specification provides considerable guidance as to how to make and assess the population of conjugate molecules for the required functional and/or structural characteristics of the claims. Thus, following the reasoning in the *In re Wands* decision, the disclosure is adequate to enable the invention as claimed.

Thus, the specification provides adequate guidance pertaining how to make and use the claimed populations of conjugate molecules. Accordingly, the pending claims are in compliance with the enablement requirements.

Written Description

Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 78, 83-84, 86 and 90-107 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this ground for rejection.

The Examiner states that "there is insufficient written description about the structure associated with function of any population of conjugate molecules or composition mentioned above because the term "antigen", "allergen", "pollen allergen" and polypeptide without SEQ ID NO: have no structure." Applicants disagree with this assertion.

Applicants respectfully submit that the specification provides a description of sufficient, relevant, identifying characteristics of the claimed populations of conjugate molecules that one skilled in the art would recognize that the inventor had possession of the claimed invention when the application was filed. The claimed populations of conjugate molecules are sufficiently and identifiably described in the specification both in terms of their structural and functional characteristics. Thus, the pending claims are fully described in the specification as filed.

With respect to the written description requirement for patentability, the burden is on the Examiner to present evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. MPEP § 2163. Applicants respectfully submit that the Examiner has failed to meet this burden. The Examiner has not provided supported reasoning why the relevant identifying characteristics of the claimed conjugate populations and the description of antigens and ISS-containing polynucleotides provided by the specification are insufficient to satisfy the written description requirement.

As outlined above, the specification provides an extensive description of the claimed invention, including ISS-containing polynucleotides, antigens, as well as the claimed populations of conjugate molecules composed of the polynucleotide and the antigen. The specification also describes many species of ISS-containing polynucleotides and many species of antigen appropriate for use in the claimed conjugate molecules.

Applicants respectfully submit that the pending claims are fully described in the application as filed. Accordingly, Applicants respectfully request that this ground for rejection be withdrawn.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of claims under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 50, 51, 60, 61, 71, 72, 83 and 84 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

The Examiner states that the "recitation of "G-3'" in claims 50 has no antecedent basis in base claim 45 because the word "G", which is a purine at the 3' end is not recited in claim 45."

Office Action, page 10, section 11. Applicants respectfully point out that the sequence recited in claim 50 includes the sequence recited in claim 45 plus two additional bases at the 3' end, C and G. Thus, the sequence of claim 50 has antecedent basis in claim 45. The immunostimulatory sequence of claim 45 comprises the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine-3'. The immunostimulatory sequence of claim 50 depends from claim 45 and further includes two additional bases, C and G, at the 3' end of the 5'-purine, purine, C, G, pyrimidine, pyrimidine-3' sequence of claim 45. Accordingly, the sequence of claim 50 has proper antecedent basis in claim 45.

The Examiner also states that "[c]laim 45 should depends on claim 1." Applicants respectfully point out that claims 45 and 43 have a relationship similar to that of claims 50 and 45. The immunostimulatory sequence of claim 43 comprises the sequence 5'-cytosine, guanine-3'. The immunostimulatory sequence of claim 45 depends from claim 43 and further includes two additional purines 5' and two additional pyrimidines 3' to the 5'-cytosine, guanine-3' sequence of claim 43. Accordingly, the sequence of claim 45 has proper antecedent basis in claim 43.

The rejection of claims 60, 71 and 83 and the statements that claims 45, 71 and 83 should have different dependency were based on the same reasoning for that of claims 50 and 45. Although Applicants have herein amended dependency of claim 56, Applicants respectfully disagree with the premise of these rejections. As outlined above, Applicants submit that the sequences of the rejected claims, as well as claims 45, 55, 71 and 83, have proper antecedent basis and that the claim dependency is correct.

In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 50, 51, 60, 61, 71, 72, 83 and 84 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. § 102(b)

Claims 1-3, 50-51, 60-61, 71-72, 75, 83-84, 86, and 90-107 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 98/16247, Carson et al. ("Carson"). Applicants respectfully traverse this rejection.

As outlined herein, the claimed invention is directed to populations of conjugate molecules with particular structural and functional characteristics. In order to anticipate, a reference must disclose each and every element of a claimed invention. By rejecting the claims under 35 U.S.C. § 102(b), the Examiner alleges that Carson teaches all the limitations of the examined claims. Applicants respectfully traverse this assertion.

Carson describes ISS-antigen conjugates made at a ratio of 5:1 (ISS to antigen) and demonstrates that such conjugates stimulate a Th1-type immune response to the antigen upon administration, including increasing production of antigen-specific IgG2a and decreasing production of antigen-specific IgE. However, Carson does not teach the claimed invention. Carson does not describe that the ISS-antigen conjugates were conjugated such that the ratio of conjugate to antigen required for 50% inhibition of antigen-specific antibody to antigen binding is about 3.5 to about 6.0. Carson does not describe that the ISS-antigen conjugates were conjugated such that the extent of antigen and polynucleotide conjugation provides a 40% histamine release ratio of greater than about 500. Carson does not describe that the ISS-antigen conjugates were conjugated such that the extent of antigen and polynucleotide conjugation provides an average of at least 5.5 of the polynucleotides per antigen molecule. Carson does not describe that the ISS-antigen conjugates were conjugated such that the extent of antigen and polynucleotide conjugation provides an average ratio of average polynucleotide mass to average antigen mass of at least 1.1.

In support of the rejection of claim 63 in view of Carson, the Examiner states that the "recitation of "**an average** of at least 5.5 ISS containing polynucleotides per antigen molecule (5.5:1 ration)" in claim 63 would include the reference conjugate at 5:1 (ISS:antigen) ratio, since

some of claimed conjugate in the population is 5:1 ratio, some are at 6:1 ratio and others are at 4:1 ratio." Office Action, page 11, emphasis original.

Claim 63 is directed to a population of conjugate molecules wherein the extent of conjugation provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule. Applicants respectfully point out that Carson teaches conjugate molecules made at 5:1 (ISS: antigen) and, even if the preparation of conjugate molecules of Carson were to contain some molecules at 6:1 and others at 4:1 (although this is not stated by Carson), Carson does not teach that the average in the population is at least 5.5 ISS-containing polynucleotides per antigen molecule. Thus, Carson does not anticipate claim 63.

Apparently with regard to claims 1 and 2, the Examiner states that the "inhibition of binding to higher titer of IgG2a, (See Fig 3, IgE-ISS of the WO98/1627) and lower antigen specific IgE, in turn lower histamine release due to anti-IgE crosslinks to Fc receptors on mass cell or basophils are the inherent properties of the reference conjugate." Office Action, page 12.

As noted above, Carson describes an increase in IgG2a and a decrease in IgE in response to administration of the ISS-antigen conjugates. However, the presently rejected claims are not directed to blocking antibody binding or histamine release upon administration of the conjugate populations. Claim 1 is directed to a population of conjugate molecules where the extent of conjugation is such that the ratio of concentration of conjugate to concentration of antigen required for 50% inhibition of antigen-specific antibody to antigen binding is about 3.5 to about 6.0. Claim 2 is directed to a population of conjugate molecules where the extent of conjugation is such that the extent of antigen and polynucleotide conjugation provides a 40% histamine release ratio of greater than about 500.

The Examiner also states that "the extent of conjugation is the inherent method steps that depend on the reaction time. The shorter the reaction time, the concentration of antigen-ISS-ODN conjugate would be less and smaller (less mass)." Office Action, page 11.

With respect to the use of inherency in a rejection, the burden is on the Examiner to provide rationale or evidence tending to show inherency. M.P.E.P. § 2112. "To establish

inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the references, and that it would be so recognized by persons of ordinary skill.' " *In re Robertson*, 169 F.3d 743,745, 49 USPQ2d 1949, 1950-1951 (Fed. Cir. 1999). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessarily flows from teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990) (emphasis in original). Applicants respectfully submit that the Office Action has not provide fact or sound technical reasoning to support the statements regarding inherency in view of Carson and, thus, the Examiner has failed to meet this burden.

The present invention provides three different classes of conjugate molecules. Despite all classes being conjugate molecules of an ISS-containing polynucleotide and an antigen, the specification demonstrates that each class has different biological properties. As described above, the claimed conjugate populations of the present invention fall into the "H" class of conjugate molecules. Nothing in Carson, or in the Office Action, supports that the allegedly inherent characteristics of the claimed populations of conjugate molecules necessarily flows from Carson.

Apparently with reference to claim 75, the Examiner states that Carson "teaches that the concentration of the conjugate to the antigen is 5:1, which is at least 1.1." Office Action, pages 11 and 12. Applicants respectfully point out that Carson teaches conjugate molecules made at 5:1 ISS to antigen not conjugate to antigen. In addition, the extent of conjugation in claim 75 provides an average ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1. The average mass ratio of claim 75 is different that the molecule ratio described by Carson. Carson does not describe conjugation to an extent that provides an average mass ratio of at least 1.1.

Thus, Applicants respectfully submit that Carson fails to disclose the instant claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §102(b).

CONCLUSION

Applicants have, by way of the amendments and remarks presented herein addressed all issues that were raised in the outstanding Office Action. Applicant respectfully contends that this Amendment has overcome the rejections and that the pending claims are in condition for allowance. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001500.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the following amendments without prejudice or disclaimer.

In the Claims:

Please amend claims 1, 2, 60, 63 and 75 as follows.

1. (Amended) A population of conjugate molecules, said conjugate molecules comprising an antigen and a polynucleotide comprising an immunostimulatory sequence (ISS), wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length and wherein the extent of conjugation in the population is such that the ratio of (i) concentration of ISS-antigen conjugate required for 50% inhibition of binding of antigen-specific antibody to antigen to (ii) concentration of antigen required for 50% inhibition of antigen-specific antibody to antigen is about 3.5 to about 6.0.

2. (Twice Amended) A population of conjugate molecules, said conjugate molecules comprising an antigen and a polynucleotide comprising an immunostimulatory sequence (ISS), wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length, wherein the antigen is an allergen, and wherein the extent of conjugation in the population provides a 40% histamine release ratio of greater than about 500, said ratio calculated as the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophils from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophils from an antigen-sensitized individual.

60. (Amended) The population of claim [56] 55, wherein said immunostimulatory sequence comprises the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3'.

63. (Amended) A population of conjugate molecules, said conjugate molecules comprising an antigen and a polynucleotide comprising an immunostimulatory sequence (ISS), wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length and wherein the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule.

75. (Amended) A population of conjugate molecules, said conjugate molecules comprising an antigen and a polynucleotide comprising an immunostimulatory sequence (ISS), wherein the polynucleotide is greater than 6 and less than about 200 nucleotides in length and wherein the extent of conjugation in the population provides an average ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen of at least 1.1.